IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Robert L. CAMPBELL, et al.

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Title: METHOD OF IDENTIFYING PEPTIDES HAVING DESIRED ACTIVITY LEVELS (as amended)

Group: 1631

Examiner: Eric S. DeJong

Confirmation No.: 2590

APPELLANTS' BRIEF

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September 4, 2007

Sir:

This brief is being submitted in response to the Notice of Non-Compliant Appeal Brief mailed on August 1, 2007 and under 37 CFR §1.192 in connection with the appeal of the above-identified application, a notice of appeal having been filed June 20, 2006.

Real Party In Interest

The real party in interest is Becton, Dickinson and Company, the assignee of the present application.

Related Appeals and Interferences

A Notice of Appeal was filed on June 13, 2006 for Application No. 10/087,942, which is a Divisional of the instant application.

There are no other known appeals or interferences that will directly affect or be affected by or have a bearing on the Board's decision in the pending appeal.

Status of Claims

Claims 1 – 75, 77-81, 96 – 130, and 133 have been cancelled.

Claims 76, 82-95, 131, 132, and 134-138 are pending.

Claims 76, 82-90, 92-95, 131, 132, and 134-138 are on appeal.

Status of Amendments

An amendment has been filed cancelling claim 91. To the best of Applicants' knowledge, this amendment has not been entered or acted on by the Examiner.

Summary of Claimed Subject Matter

The claims of the instant invention are directed to a screening method, which can be used to assist in the identification of peptides possessing a desired characteristic. See, for example, Figs. 1 and 8. The screening method uses qualitative and/or quantitative data from test peptides to identify appropriate sets of candidate peptides having a particular activity, as determined by the user.

In accordance with one or more embodiments, the present invention provides a method of identifying a peptide with a desired activity having an indicia that satisfies a test requirement. A predetermined set of peptides is identified and parameterized by determining first and second parameters for each peptide. The first parameter is a whole molecule parameter, while the second parameter is dependent on the specific order of constitutive subunits within each peptide. The term "whole molecule parameter" is a value that characterizes a molecule irrespective of the arrangement of its consecutive atoms or sub-units. For example, the specification defines a whole molecule parameter for a peptide as one that does not depend on the order or sequence of the amino acids in the peptide (page 28, lines 2-6). The detailed description also provides examples of whole molecule parameters. See, for example, page 28, lines 15-21 and page 51, lines 14-16. A "sequence-specific parameter" is dependent on the specific order, or sequence, of the consecutive atoms, or sub-units. See, for example, page 28, lines 11-12.

A space-filling design is then performed for the parameterized peptides that will be used in constructing a first test peptide library. Space-filling designs are known in the art, and broadly encompass various techniques known to those skilled in the art. As discussed in the detailed description, exemplary space-filling designs

include, but are not limited to, full factorial designs, fractional factorial designs, maximum diversity libraries, genetic algorithms, coverage designs, spread design, cluster based designs, Latin Hypercube Sampling, and other optimal designs (e.g. D-Optimal), and the like. See, for example, page 19, line 15 to page 20, line 22.

According to one or more embodiments of the invention, the first test peptide library contains first test peptides having a length of about four amino acids to about twenty amino acids. Next, each first test peptide is tested so that an indicia can be measured for a desired activity. The indicia of activity is a property that can be measured using various methods known to those skilled in the art. Such methods include, but are not limited to, enzyme-linked immunosorbent assays (ELISAs), and/or labels capable of producing signals detectable by: spectrophotometry, x-ray diffraction or absorption, magnetism, enzymatic activity, chemiluminescence, fluorescence, and so forth. See, for example, page 18, lines 9-21.

A quantitative relationship is derived based on three specific properties: the measured indicia, the first parameter, and the second parameter. For example, an equation can be used to describe the relationship between the activity and parameters. See, for example, page 30, lines 19-25. The specification describes an exemplary embodiment using eight test peptides and identifies three parameters: hydrophobicity, molecular weight, and total charge. In this example, the biological activity (such as protein production) represents the indicia of activity. Using this quantitative information (qualitative information may also be used), a mathematical equation is developed to define the relationship between these three values as set forth in the equation on page 32. This equation represents the relationship between the three values of hydrophobicity (first parameter), molecular weight (second

parameter), and biological activity (indicia of activity). Alternatively, the relationship can be a quantitative structure-activity relationship (page 30, lines 26-28), conventional line-fitting algorithms (page 33, lines 9-32), or distance function relationships (see, for example, page 34).

Once the quantitative relationship is determined, it is applied to calculate (i.e., compute) an estimated indicia for each remaining peptide from the predetermined set of peptides. More particularly, identification of the relationship between these three values is applied to the development of another set of peptides. The specification describes the use of a mathematical equation (on page 32) to predict the biological activity for an untested peptide, HYPV. Specifically, a biological activity of 28.2 was predicted for the untested peptide HYPV using only its hydrophobicity and molecular weight based on the mathematical equation. If the test requirement requires a predicted activity of at least 25, then the HYPV peptide represents a good candidate for further synthesis and testing. If, on the other hand, the test requirement requires a predicted activity of at least 30, then the HYPV peptide represents a bad candidate, and the mathematical equation would be applied to predict the biological activity of other untested peptides.

It is noted that the equation is applied to estimate the indicia for peptides which were not part of the first test peptide library. Furthermore, these peptides were never tested (i.e., assayed or screened).

A test requirement is subsequently set based on the desired activity level. The test requirement is in the form of a range of test indicia values. These values can correspond to a desired range that satisfies a criteria considered to be important.

According to at least one embodiment of the invention, a subgroup of peptides having an indicia that satisfies the test requirement can be selected and expanded into their constituent compound isomers. A space-filling design is performed on the constituent compound isomers to identify candidate peptides, and an estimated indicia is calculated for each candidate peptide using the same derived relationship. The derived relationship can be optionally modified by adjusting various parameters based, in part, on the accuracy of predictions.

Next, a second test peptide library containing at least one second test peptide is selected. Only second test peptides having an estimated indicia that has been calculated to satisfy the test requirement are selected to be in the second test peptide library. Since the estimated indicia are calculated only for the remaining peptides, none of the second test peptides were present in the first test peptide library. Furthermore, none of the second test peptides have been tested (e.g., screened or assayed) at this time. At this point, the second test peptides are tested in order to actually measure the indicia. Finally, at least one second test peptide having a measured indicia that satisfies the test requirement is identified.

According to independent claim 135, a predetermined set of peptides is identified and parameterized. See, for example, page 6, line 30 to page 7, line 9 and page 27, lines 22-31. A space-filling design is then performed for the parameterized peptides that will be used in constructing a first test peptide library. See, for example, page 19, line 15 to page 20, line 22. Next, each first test peptide is tested so that an indicia can be measured for a desired activity. See, for example, page 18, lines 9-21.

According to at least one feature of independent claim 135, a quantitative relationship is derived based on three specific properties: the measured indicia, the first parameter, and the second parameter. See, for example, equation on page 32; page 30, lines 26-28; page 33, lines 9-32; and page 34. Once the quantitative relationship is determined, it is applied to calculate (i.e., compute) an estimated indicia for each remaining peptide from the predetermined set of peptides. See, for example, page 32. It is noted that these peptides were not part of the first test peptide library. A test requirement is subsequently set based on the desired activity level. See, for example, page 26, line 18 to page 27, line 5 and page 31, line 3 to page 33, line 8. The test requirement is in the form of a range of test indicia values. These values can correspond to a desired range that satisfies a criteria considered to be important.

Next, a second test peptide library containing at least one second test peptide is selected. See, for example, page 33, line 25 to page 34, line 12. Only second test peptides having an estimated indicia that has been calculated to satisfy the test requirement are selected to be in the second test peptide library. Since the estimated indicia are calculated only for the remaining peptides, none of the second test peptides are present in the first test peptide library. Furthermore, none of the second test peptides have been tested (e.g., screened or assayed) as this time. See, for example, page 29, lines 10-13. At this point, the second test peptides are tested in order to actually measure the indicia. Finally, at least one second test peptide having a measured indicia that satisfies the test requirement is identified. See, for example, page 38, lines 17-19 and page 38, line 18 to page 39, line 34.

According to independent claim 136, a predetermined set of peptides is identified and parameterized. See, for example, page 6, line 30 to page 7, line 9 and page 27, lines 22-31. A space-filling design is then performed for the parameterized peptides that will be used in constructing a first test peptide library. See, for example, page 19, line 15 to page 20, line 22. Next, each first test peptide is tested so that an indicia can be measured for a desired activity. See, for example, page 18, lines 9-21.

According to independent claim 136, a quantitative relationship is derived based on three specific properties: the measured indicia, the first parameter, and the second parameter. See, for example, equation on page 32; page 30, lines 26-28; page 33, lines 9-32; and page 34. Next, a test requirement is set based on a desired activity. See, for example, page 26, line 18 to page 27, line 5 and page 31, line 3 to page 33, line 8. The test requirement is in the form of a test indicia range. A subgroup of first test peptides having an indicia that satisfies the test requirement is selected.

The first test peptides in the subgroup are expanded into their constituent compound isomers, and a space-filling design is performed to identify candidate peptides. See, for example, page 45, line 3 to page 46, line 4. The quantitative relationship is applied to calculate an estimated indicia for each candidate peptide. See, for example, equation on page 32; page 30, lines 26-28; page 33, lines 9-32; and page 34. Next, a second test peptide library containing at least one second test peptide is selected. See, for example, page 33, line 25 to page 34, line 12. Only second test peptides having an estimated indicia that has been calculated to satisfy the test requirement are selected to be in the second test peptide library. None of

the second test peptides are present in the first test peptide library, and none have been tested as this time. See, for example, page 29, lines 10-13. The second test peptides are then tested so that the actual indicia can be measured. Finally, at least one second test peptide having a measured indicia that satisfies the test requirement is identified. See, for example, page 38, lines 17-19 and page 38, line 18 to page 39, line 34.

According to independent claim 137, a plurality of initial peptides having a length of about four amino acids to about twenty amino acids are identified and parameterized. See, for example, page 25, lines 26-30; page 6, line 30 to page 7, line 9; and page 27, lines 22-31. A space-filling design is then performed for the parameterized peptides to construct a first test peptide library. See, for example, page 19, line 15 to page 20, line 22. The first test peptide library contains first test peptides that are a subset of the initial peptides. Next, each first test peptide is tested so that an indicia can be measured for a desired activity. See, for example, page 18, lines 9-21.

A quantitative relationship is derived based on three specific properties: the measured indicia, the first parameter, and the second parameter. Once the quantitative relationship is determined, it is applied to calculate an estimated indicia for each initial peptide. See, for example, equation on page 32; page 30, lines 26-28; page 33, lines 9-32; and page 34. A test requirement in the form of a test indicia range is set based on the desired activity level. See, for example, page 26, line 18 to page 27, line 5 and page 31, line 3 to page 33, line 8. Next, a second test peptide library containing at least one second test peptide is selected. See, for example, page 26, line 18 to page 27, line 5 and page 31, line 3 to page 33, line 8. The

second test peptides are not in the first test peptide library and contain an estimated indicia that satisfies the test requirement. See, for example, page 29, lines 10-13. The second test peptides are tested in order to measure the indicia, and at least one second test peptide having a measured indicia that satisfies the test requirement is identified. See, for example, page 38, lines 17-19 and page 38, line 18 to page 39, line 34.

Independent claim 138 defines a method of identifying a peptide with a desired activity having an indicia that satisfies a test requirement. A predetermined set of peptides is identified and parameterized. See, for example, page 6, line 30 to page 7, line 9 and page 27, lines 22-31. A space-filling design is then performed for the parameterized peptides that will be used in constructing a first test peptide library. See, for example, page 19, line 15 to page 20, line 22. Next, each first test peptide is tested so that an indicia can be measured for a desired activity. See, for example, page 18, lines 9-21.

According to independent claim 138, a quantitative relationship is derived based on three specific properties: the measured indicia, the first parameter, and the second parameter. Once the quantitative relationship is determined, it is applied to calculate an estimated indicia for each remaining peptide from the predetermined set of peptides. See, for example, equation on page 32; page 30, lines 26-28; page 33, lines 9-32; and page 34. A test requirement is subsequently set based on the desired activity level. The test requirement is in the form of a range of test indicia values. See, for example, page 26, line 18 to page 27, line 5 and page 31, line 3 to page 33, line 8. Next, a second test peptide library containing at least one second test peptide is selected. See, for example, page 26, line 18 to page 27, line 5 and

page 31, line 3 to page 33, line 8. Only second test peptides having an estimated indicia that satisfies the test requirement are selected to be in the second test peptide library. None of the second test peptides are present in the first test peptide library, and none have been tested. See, for example, page 29, lines 10-13. At this point the second test peptides are tested in order to actually measure the indicia. Finally, at least one second test peptide having a measured indicia that satisfies the test requirement is identified. See, for example, page 38, lines 17-19 and page 38, line 18 to page 39, line 34.

Grounds of Rejection to be Reviewed on Appeal

I. Whether Claims 76, 82, 87-90, 92-95, 131, 132, and 134-135 are unpatentable under 35 U.S.C. §102(b) over Ostrem et al. ("(Ostrem").

II. Whether Claims 76, 82-90, 92-95, 131, 132, and 134-138 are unpatentable under 35 U.S.C. §103(a) over Ostrem in view of U.S. Patent 6,240,374 to Cramer et al. ("Cramer").

Grouping of Claims

Claims 135 – 138 are independent.

Claims 76 and 82 – 90 and 92 – 95 stand or fall together with independent claim 135.

Claims 131, 132, and 134 stand or fall together with independent claim 137.

Argument

Claims 76, 82, 87-90, 92-95, 131, 132, and 134-135 stand rejected under 35 U.S.C. §102(b) as being anticipated by Ostrem. Claims 76, 82-90, 92-95, 131, 132, and 134-138 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Ostrem in view of Cramer.

For the reasons set forth below, these rejections should be reversed.

I. Claims 76, 82, 87-90, 92-95, 131, 132, and 134-135 Are Patentable Over Ostrem

Claims 76, 82, 87-90, 92-95, 131, 132, and 134-135 are not anticipated by Ostrem. The rejection of these claims under 35 U.S.C. §102(b) is improper. Additionally, Ostrem fails to disclose all of the features recited in these claims.

A. The rejection of Claims 76, 82, 87-90, 92-95, 131, 132, and 134-135 under 35 U.S.C. §102(b) is improper

The Examiner fails to make a *prima facie* case of anticipation predicated on the teachings of Ostrem. The burden falls on the Examiner to establish a *prima facie* case of anticipation. See *In re Sun*, 31 USPQ2d 1451, 1453 (Fed. Cir. 1993). As emphasized by the court in *In re Warner*, "[t]he precise language of 35 U.S.C. 102 that "a person shall be entitled to a patent unless," concerning novelty and unobviousness, clearly places a burden of proof on the Patent Office which requires it to produce the factual basis for its rejection of an application under sections 102 and 103. . . ." (Emphasis added) 154 USPQ 173, 177 (C.C.P.A. 1967), *cert. denied*, 389 U.S. 1057 (1968).

In order to qualify as an anticipatory reference, a prior art reference must necessarily disclose each and every element recited in the claimed invention. This disclosure must also be made with a sufficient level of clarity. See *Motorola, Inc. v. Interdigital Tech. Corp.*, 121 F.3d 1461, 43 USPQ2d 1481, 1490 (Fed. Cir. 1997). See also *In re Spada*, 911 F.2d 705, 708, 15 USPQ2d 1655, 1657 (Fed. Cir. 1990) ("[T]he [prior art] reference must describe the applicant's claimed invention sufficiently to have placed a person of ordinary skill in the field of the invention in possession of it." (citations omitted)). As further stated by the Federal Circuit, "Although this disclosure requirement presupposes the knowledge of one skilled in the art of the claimed invention, that presumed knowledge does not grant a license to read into the prior art reference teachings that are not there." (Emphasis added) *Id.*

Reference is further made to the decision of *In re Robertson*, 49 USPQ 2d 1949 (Fed. Cir. 1999), wherein the court pointed out that anticipation under 35 U.S.C. §102 requires that each and every element as set forth in the claim be found, either expressly or inherently described in a single prior art reference. As noted by that court, if the prior art reference does not expressly set forth a particular element of the claim, that reference still may anticipate if the element is "inherent" in its disclosure. To establish inherency, the extrinsic evidence "must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill." (Emphasis added). Moreover, the court pointed out that inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient. See also *In re Oelrich,*

666 F.2d 578, 581, 212 USPQ 323, 326 (C.C.P.A. 1981) ("Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing *may* result from a given set of circumstances is not sufficient.")

Finally, the alleged anticipatory reference must be enabling. In particular, it is the claimed invention that must be enabled within the reference and not any other teachings disclosed by the reference. See *Elan Pharms. Inc. v. Mayo Found. for Med. Educ. & Research*, 346 F.3d 1051, 68 USPQ2d 1373, 1375-76 (Fed. Cir. 2003) ("To serve as an anticipating reference, the reference must enable that which it is asserted to anticipate."); and *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1354, 65 USPQ2d 1385, 1416 (Fed. Cir. 2003) ("A claimed invention cannot be anticipated by a prior art reference if the allegedly anticipatory disclosures cited as prior art are not enabled.").

B. Ostrem fails to disclose all of the features recited in these claims.

Independent Claim 135

Independent claim 135 of the instant invention defines a method of identifying a peptide with a desired activity having an indicia that satisfies a test requirement. The method comprises the steps of:

> identifying a predetermined set of peptides;
>
> parameterizing the predetermined set of peptides by:
>
> determining a first parameter for each predetermined peptide, wherein the first parameter is a whole molecule parameter, and
>
> determining a second parameter for each predetermined peptide, wherein the second parameter is dependent on the specific order of constitutive subunits within each predetermined peptide;
>
> performing a space-filling design of the parameterized peptides to identify first test peptides;

constructing a first test peptide library comprising a plurality of first test peptides identified using the space-filling design, wherein the length of said first test peptides comprises about four amino acids to about twenty amino acids, and wherein said first test peptides are a subset of said predetermined set of peptides;

determining an activity, having an indicia, of said plurality of first test peptides;

measuring the indicia of said activity for said plurality of first test peptides;

deriving a quantitative relationship between said indicia of said activity, said first parameter, and said second parameter;

calculating an estimated indicia for each remaining peptide from said predetermined set of peptides using said quantitative relationship;

setting a test requirement, based on a desired activity, having a test indicia range;

selecting a second test peptide library comprising at least one second test peptide, wherein each second test peptide has an estimated indicia that satisfies said test requirement, and wherein said second test peptides are not in said first test peptide library;

measuring the indicia of each second test peptide; and

identifying at least one second test peptide having a measured indicia that satisfies said test requirement.

According to independent claim 135, a predetermined set of peptides is identified and parameterized by determining first and second parameters for each peptide. The first parameter is a whole molecule parameter while the second parameter is dependent on the specific order of constitutive subunits within each peptide. A space-filling design is then performed for the parameterized peptides that will be used in constructing a first test peptide library. Next, each first test peptide is tested so that an indicia can be measured for a desired activity.

According to at least one feature of independent claim 135, a quantitative relationship is derived based on three specific properties of each peptide: the measured indicia, the first parameter, and the second parameter. Once the quantitative relationship is determined, it is applied to calculate (i.e., compute) an

estimated indicia for each remaining peptide from the predetermined set of peptides. It is noted that these peptides were not part of the first test peptide library. Furthermore, these peptides were never tested (i.e., assayed or screened). A test requirement is subsequently set based on the desired activity level. The test requirement can be in the form of a range of test indicia values. These values can correspond to a desired range that satisfies a criteria considered to be important.

Next, a second test peptide library containing at least one second test peptide is selected. Only second test peptides having an estimated indicia that has been calculated to satisfy the test requirement are selected to be in the second test peptide library. Since the estimated indicia are calculated only for the remaining peptides, none of the second test peptides are present in the first test peptide library. Furthermore, none of the second test peptides have been tested (e.g., screened or assayed) as this time. At this point, the second test peptides are tested in order to actually measure the indicia. Finally, at least one second test peptide having a measured indicia that satisfies the test requirement is identified.

The method defined by claim 135 advantageously reduces the amount of experimentation required to identify peptides having a desired indicia, as discussed in the "Background" section of the application. This reduction can directly translate to a reduction in time and costs associated with identifying such peptides. Additionally, it is possible to generate a substantially large group of candidate peptides that could potentially have an indicia which satisfies the test requirement. As can be appreciated, it is not cost effective, efficient, or convenient to test a large number (e.g., over one million) peptides. The candidate peptides can therefore be filtered to a smaller number of second test peptides that will actually be tested by

properly setting the test requirement. Consequently, the number of actual experiments conducted can be significantly reduced.

The Examiner alleges that Ostrem anticipates the claimed invention. In support of this position, the Examiner identifies various claim steps that are allegedly disclosed by Ostrem. As discussed in greater detail below, the Examiner appears to have misconstrued some of the claimed steps and omitted others. Consequently, there is no showing of where, or how, Ostrem discloses each step recited in the claimed invention.

Ostrem discloses a library for screening of biotinylated factor Xa-SAP mixture added to library beads. Beads that showed a blue color were destained, stripped, and further screened with the factor Xa-SAP-inhibitor mixture. Ostrem identifies certain factor Xa inhibitors from an initial combinatorial library based on results obtained by assaying the beads. The most comprehensive listing of peptides in Ostrem appears to be presented in Table 1, which does not include any peptide isomers (comprised of the same amino acids but varying in sequence). Ostrem itself discloses that a complete representation of peptides in the library was not known, as only a select few peptides were confirmed as being available after activity assays were completed. ("Beads picked from the library which showed no staining when incubated with active-site inhibited factor Xa under these conditions were briefly stripped and destained, then incubated with uninhibited factor Xa and SAP. Beads which restained were submitted for sequencing by Edman degradation. Peptides were resynthesized based on sequences obtained from individual beads." Page 1054, col.1, lines 45-51).

Another indication that the complete set of peptides in Ostrem's library screening procedure was not known is the "split-synthesis methodology" used to generate the peptides. As is known, such methods are used when the intent is to screen first and confirm the presence of peptides later. Typically, split synthesis methods are used when the goal is to synthesize and assay large libraries of peptides in a batch format. Such an approach does not attempt to take advantage of group isomers and does not attempt to account for any specific peptide(s) before assaying. Indeed the cost and time associated with confirming each peptide in the test library is prohibitive. Ostrem's selection of the split-synthesis method clearly supports the fact that a space-filling design was not applied.

The only measurements taken by Ostrem appear to relate to the potency of the peptides. This value, however, is different from the first and second parameters measured in the claimed invention, and in fact appears to be more consistent with measurement of an activity level. Ostrem measures the increased potency range of the initial leads identified in the combinatorial library. They are not calculated from a derived relationship as set forth in the claims.

Review of Ostrem reveals a process (however useful) that is clearly different from that recited in the claimed invention. According to Ostrem, various amino acids on peptide bound beads are assayed in order to measure inhibition of factor Xa activity. Ostrem appears to assay peptides attached to the same beads used in synthesis rather than peptides cleaved from the solid support.

The Examiner alleges that Ostrem provides an enabling disclosure, and that no factual evidence to the contrary has been presented. However, the validity of Ostrem's results have never been questioned or challenged. Only Ostrem's failure

to disclose specific features recited in the claims are at issue. The Examiner's position is legally incorrect, because the anticipatory reference is required to enable the claimed invention against which it is being applied, not just any process the Examiner chooses to believe must be enabled. See *Amgen, Inc. v. Hoechst Marion Roussel, Inc.* Therefore, it is not necessary to provide any factual evidence challenging the validity of Ostrem's procedures and results, since they clearly differ from the claimed invention.

Ostrem simply fails to enable the claimed invention. Ostrem provides a disclosure that enables identification of a family of factor Xa inhibitors. While this process may have its own utility and usefulness, it is clearly different from the claimed invention. Further, regardless of the Examiner's opinion, Ostrem is required to enable the claimed invention.

The Examiner alleges that Ostrem discloses the step of parameterizing the predetermined set of test peptides because peptides of amino acids in length are evaluated as having a potency of 4 to 15 μm and retain an unusual selectivity for factor Xa over thrombin. Regardless of the Examiner's assumptions, however, there is no factual disclosure in Ostrem to support parameterizing the predetermined set of peptides as recited in the claimed invention and supported by the specification.

Ostrem fails to disclose the claimed feature of parameterizing the predetermined peptides through determination of first and second parameters. Determining a peptide length of 8 amino acids simply cannot be interpreted as reading on the claimed the step of determining a second parameter which depends on the specific order of constitutive subunits within each desired peptide. Ostrem only measures to the potency of the peptides. This value, however, is different from

the first and second parameters measured in the claimed invention, and in fact appears to be more consistent with measurement of an activity level.

The Examiner states that Ostrem discloses construction of a combinatorial library of peptides as containing a multitude of varying peptide sequences in order to investigate changes peptide properties that can be correlated to specific sequences. The Examiner concludes that this disclosure, in part, reads on the claimed step of constructing a first test peptide library comprising a plurality of first test peptides identified using the space-filling design. The Examiner further alleges that a space-filling design has not be defined in the specification.

Applicants note, however, that this was discussed during the interview of June 20, 2005. The specification clearly provides adequate support for the terminology, as noted in Applicants' Amendment filed on December 16, 2004 (see pages 34 and 37-38 thereof).

The Examiner relies on Ostrem for disclosing construction of a combinatorial library of peptides as containing a multitude of varying peptide sequences in order to investigate changes in peptide properties that can be correlated to specific sequence changes. The Examiner concludes that such a disclosure provides a space-filling model wherein variations of octamer peptides have been explored in both sequence and conformational space context. However, it is unclear where this is actually stated in the reference. Additionally, Ostrem's library is necessarily biased toward factor Xa inhibitors, and clearly not representative of the octamer peptide space. In fact, there is nothing in Ostrem to indicate that an attempt was being made to represent the entire octamer peptide space.

Ostrem fails to construct a first test peptide library designed to provide any organized representation of, for example, the total octamer space. Ostrem does not even appear to mention a space-filling design or provide some suggestion for a design that selects representatives from a plurality of compound isomers. Ostrem provides a listing of peptides in Table 1, which does not include any peptide isomers (comprised of the same amino acids but varying in sequence). Ostrem itself discloses that a complete representation of peptides in the library was not known, as only a select few peptides were confirmed as being available after activity assays were completed. ("Beads picked from the library which showed no staining when incubated with active-site inhibited factor Xa under these conditions were briefly stripped and destained, then incubated with uninhibited factor Xa and SAP. Beads which restained were submitted for sequencing by Edman degradation. Peptides were resynthesized based on sequences obtained from individual beads." Page 1054, col.1, lines 45-51).

Another indication that the complete set of peptides in Ostrem's library screening procedure was not known is the "split-synthesis methodology" used to generate the peptides. Split synthesis methods are used when the goal is to synthesize and assay large libraries of peptides in a batch format. As previously stated, such an approach does not attempt to take advantage of group isomers and does not attempt to account for any specific peptide(s) before assaying. Indeed the cost and time associated with confirming each peptide in the test library would be prohibitive. Ostrem's selection of the split-synthesis method clearly shows that a space-filling design was not applied.

Similarly, Ostrem provides no disclosure or suggestion for deriving a quantitative relationship between the measured indicia, the first parameter, and the second parameter, since these parameters are not measured. Ostrem merely tests peptides attached to the same beads. Ostrem does not provide any indication of how the inhibition of factor Xa activity relates to the first parameter or the second parameter. Furthermore, Ostrem never discusses a single formula that has been derived or any values that are calculated (not measured through assays) using this formula. Ostrem merely measures quantities such as the inhibition of Xa activity, and plots them in various graphs. Ostrem does not contain a single quantitative formula that is representative of these graphs.

Ostrem appears to assay peptides attached to the same beads used in synthesis. In contrast, all of the screening applicable to the claimed invention uses peptides cleaved from the solid support. Peptides in their free form can be assayed for performance "in solution" and "immobilized to standard tissue culture surfaces. It is difficult to see how Ostrem could have used peptides attached to a synthesis resin in a screen for peptides intended to enhance culture media. It is even more difficult to see how one skilled in the art could have applied the methods of Ostrem to the development of a process for enhancing culture media. In many cases peptides in a cell culture environment must cross the cell outer membrane before having an impact. The contribution from a peptide immobilized to a synthesis bead would certainly be biased.

Regardless of the Examiner's interpretation of Ostrem, mere testing of peptides attached to the same beads is a far cry from derivation of an actual quantitative formula that can be used to model the relationship between the indicia,

first parameter, and second parameter, as set forth in the claimed invention. Ostrem does not provide an indication of how the inhibition of factor Xa activity relates to the first parameter or the second parameter. The Examiner directs attention to various plots as disclosing the claimed steps of deriving and applying a quantitative relationship. However, Ostrem never discusses a single formula that has been derived or any values that are calculated (not measured through assays) using this formula. In fact, Ostrem appears to be completely silent on applying a quantitative formula to predict the potency of untested peptides. Applicants emphasize that the derived relationship is based on three specific factors, namely the indicia, first parameter, and second parameter. The Examiner uses hindsight to misconstrue the teachings of Ostrem to read on the claimed invention. The simple fact is that Ostrem fails to disclose derivation and application of any quantitative relationships.

The Examiner further states, in part, that Ostrem performs four separate assays wherein peptide-bound beads are separately prepared and used in each of the four distinct assays. The selection of peptides based on the results of these assays purportedly reads on various steps of the claimed invention.

This particular analogy appears contrary to the claimed steps, and actually teaches away from the present invention. As set forth in the claimed invention, once a quantitative relationship has been derived, an estimated indicia is calculated (using the derived relationship) for peptides that have not been previously screened. Calculation of the estimated indicia is intended to reduce the number of test/assays performed. This allows consideration of an extremely high number of peptides in predicting those which may have the desired level of activity.

By the Office Action's own admission, Ostrem does exactly the opposite. Specifically, as indicated in the Office Action, Ostrem performs four separate assays of peptides identified from the initial set. Accordingly, Ostrem performs actual experiments on these peptides. It is unclear of how performing assays of peptides could possible read on, or even remotely suggest, calculating an estimated indicia using a derived quantitative relationship. In fact, performing additional experiments is contradictory to the intention of the claimed invention to reduce the actual number of experiments. This clearly teaches away from the claimed invention.

Furthermore, the estimated indicia is calculated for peptides that remain from the predetermined set of peptides, i.e., peptides which are not included from the first test peptide library and have not yet been tested. In contrast, Ostrem never goes outside the original combinatorial library to identify peptides that have not been assayed and calculate an estimated value for the inhibition factor of Xa activity prior to performing an assay. In fact, Ostrem is completely silent about calculating and/or estimating any values. Applicants note that silence cannot be construed by the Examiner as actually disclosing a claimed step.

Additionally, the step of setting a test requirement is intended to identify candidates that have an estimated indicia which satisfies a desired level of activity. Accordingly, the test requirement must necessarily be set prior to testing the peptides. As indicated by the Examiner, the peptides in Ostrem are selected as a result of the assay, and not prior to assaying.

The Examiner alleges that these steps are not recited in the claims. However, independent claim 135, for example, clearly states that the first test peptide library is a subset of the predetermined set of peptides. Further, the claim recites calculating

an estimated indicia for each remaining peptide from the predetermined set of peptides. The derived formula is clearly applied to untested peptides. Additionally, it would be nonsensical to calculate an estimated indicia for peptides when an accurate measurement has already been obtained through assaying. Applicants further submit that this particular feature was discussed during the interview of June 20, 2005 wherein the Examiner agreed that this feature was not disclosed by Ostrem. Notwithstanding this fact, the Examiner has not shown where Ostrem applies a derived formula to predict the activity level of untested peptides.

There simply is no disclosure, or even suggestion, in Ostrem to indicate that a quantitative relationship is ever derived and subsequently applied to estimate parameters such as the inhibition of factor Xa activity prior to performing an assay of the peptide bound beads. Thus, there can be no realistic analogy to the claimed invention. Further, there are not citations to the exact location where Ostrem allegedly discloses the steps recited in the claimed invention. As previously indicated, an anticipatory reference must be enabling and must disclose all the claimed steps. The entire anticipation analysis presented in the Office Action appears tantamount to an application of the claims themselves as a blueprint to sustain and justify the rejection.

Ostrem indicates that the initial peptides selected showed measurable performance characteristics when assayed in vitro. However, these same peptides failed to perform in their intended in vivo application and the core motif required further modification to yield a functional peptide. As stated by Ostrem, "[A]lthough potent in chromogenic activity assays and *in vitro* coagulations assays, initial experimental work looking at half-life in rats following *i.v.* bolus injections showed

that *N*-acyl, *N*-akyl peptides were inactivated or cleared from plasma within1-2 minutes." See page 1057, column 1, lines 5-9. In contrast peptides derived from the claimed process are capable of performing in their intended application without further modification. The disclosure of Ostrem cannot be considered enabling.

Ostrem simply fails to either disclose or suggest features that are explicitly recited in the claimed invention, such as:

> deriving a quantitative relationship between said indicia of said activity, said first parameter, and said second parameter;
>
> calculating an estimated indicia for each remaining peptide from said predetermined set of peptides using said quantitative relationship;
>
> setting a test requirement, based on a desired activity, having a test indicia range;
>
> selecting a second test peptide library comprising at least one second test peptide, wherein each second test peptide has an estimated indicia that satisfies said test requirement, and wherein said second test peptides are not in said first test peptide library;

Accordingly, Ostrem fails to anticipate independent claim 135, and the rejection of independent claim 135 is believed to be improper under 35 U.S.C. §102(b).

Claims 76, 82, 87-90, and 92-95

Claims 76, 82, 87-90, and 92-95 depend from independent claim 135, and are believed to be allowable for the reasons set forth with respect to independent claim 135.

Independent Claim 136

Independent claim 136 defines a method of identifying a peptide with a desired activity having an indicia that satisfies a test requirement. The method

comprises, in part, the steps of:

> ...
>
> deriving a quantitative relationship between said indicia of said activity, said first parameter, and said second parameter;
>
> ...
>
> calculating an estimated indicia for each candidate peptide using said quantitative relationship;
>
> selecting a second test peptide library comprising at least one second test peptide, wherein each second test peptide is a candidate peptide having an estimated indicia that satisfies said test requirement, and wherein said second test peptides are not in said first test peptide library;
>
> ...

Independent claim 136 recites steps that are somewhat similar to those recited in independent claim 135. These steps are also not shown or suggested by Ostrem. Specifically, independent claim 136 recites a step of deriving a quantitative relationship between the indicia of activity, a first parameter, and a second parameter. As previously discussed, Ostrem fails to disclose any quantitative relationships. Independent claim 136 also recites a step utilizing this derived quantitative relationship to calculate an estimated indicia for peptides that have not been tested. Independent claim 136 also utilizes the estimated indicia in setting a test requirement to identify peptides that will actually be tested. Ostrem fails to provide any disclosure or suggestion for these features.

The Examiner alleges that Ostrem utilizes biotin labeled protein to attach peptides from libraries to beads, and thus produce a library of bead-bound peptides. The beads are subsequently assayed for activity against purified proteins and result in the identification of peptides with a desired property. This purportedly reads on the claimed step of expanding the first test peptides into compound isomers and

performing a space-filling design on the constituent compound isomers to identify candidate peptides.

The Examiner, however, overlooks key features of independent claim 136 as, described above. The statute requires disclosure of all claim features in a single reference. However, Ostrem fails to provide disclosure or suggestion for claimed features such as deriving a quantitative relationship (between the indicia of activity, the first parameter, and the second parameter), applying the derived relationship to untested peptides, and utilizing the estimated indicia to identify peptides that will actually be tested.

Accordingly, Ostrem fails to anticipate independent claim 136, and the rejection of this claim is believed to be improper under 35 U.S.C. §102(b).

Independent Claim 137

Independent claim 137 defines a method of identifying a peptide with a desired activity having an indicia that satisfies a test requirement. The method comprises, in part, the steps of:

> ...
>
> deriving a quantitative relationship between said indicia of said activity, said first parameter, and said second parameter of said plurality of test peptides;
>
> calculating an estimated indicia for each initial peptide using said quantitative relationship;
>
> ...
>
> selecting a second test peptide library comprising at least one second test peptide, wherein each second test peptide has an estimated indicia that satisfies said test requirement, and wherein said second test peptides are not in said first test peptide library;
>
> ...

Independent claim 137 also recites steps that are similar to those recited in independent claim 135. Specifically, independent claim 137 recites a step of deriving a quantitative relationship between the indicia of activity, a first parameter, and a second parameter. The derived quantitative relationship is also used to calculate an estimated indicia for peptides that have not been tested. Independent claim 137 claim also utilizes the estimated indicia in setting a test requirement to identify peptides that will actually be tested. As previously discussed, Ostrem simply does not provide any disclosure or suggestion for these features.

Accordingly, Ostrem fails to anticipate independent claim 137, and is the rejection of this claim believed to be improper under 35 U.S.C. §102(b).

Claims 131, 132, and 134

Claims 131, 132, and 134 depend from independent claim 137, and are believed to be allowable for the reasons set forth with respect to independent claim 137.

Independent Claim 138

Independent claim 138 defines a method of identifying a peptide with a desired activity having an indicia that satisfies a test requirement. The method comprises, in part, the steps of:

> ...
>
> deriving a quantitative relationship between said indicia of said activity, said first parameter, and said second parameter;
>
> calculating an estimated indicia for each remaining peptide from said predetermined set of peptides using said quantitative relationship;
>
> ...
>
> selecting a second test peptide library comprising at least one second test peptide, wherein each second test peptide has an

estimated indicia that satisfies said test requirement, and wherein said second test peptides are not in said first test peptide library;

...

Independent claim 138 recites steps that are somewhat similar to those recited in independent claim 135. For example, independent claim 138 recites a step of deriving a quantitative relationship between the indicia of activity, a first parameter, and a second parameter. The derived quantitative relationship is used to calculate an estimated indicia for peptides that have not been tested. Independent claim 138 also utilizes the estimated indicia in setting a test requirement to identify peptides that will actually be tested. As previously discussed, Ostrem simply does not provide any disclosure or suggestion for these features.

Accordingly, Ostrem fails to anticipate independent claim 138, and the rejection of this claim is believed to be improper under 35 U.S.C. §102(b).

II. Claims 76, 82-90, 92-95, 131, 132, and 134-138 are patentable over Ostrem in view of Cramer

Claims 76, 82-90, 92-95, 131, 132, and 134-138 are not obvious over Ostrem in view of Cramer. The rejection of these claims under 35 U.S.C. §103(a) is improper. Additionally, Ostrem and Cramer fail to disclose or suggest all of the features recited in these claims.

A. The rejection of claims 76, 82-90, 92-95, 131, 132, and 134-138 under 35 U.S.C. §103(a) is improper

A *prima facie* case of obviousness requires that three basic criteria be met. First, there must be some suggestion, or motivation, in the primary reference to modify, combine, or seek out the teachings of a secondary reference. Second, there

must be a realistic expectation of success from combining the two references. Finally, the prior art references must clearly teach or suggest all the claim limitations. See M.P.E.P. §706.02(j). In supporting such requirements, the Federal Circuit has held that "[i]n proceedings before the Patent and Trademark Office, the Examiner bears the burden of establishing a *prima facie* case of obviousness based upon the prior art." *In re Fritch*, 972 F.2d 1260, 23 USPQ 2d 1780 (Fed. Cir. 1992).

In the decision of *In re Fine*, 5 USPQ 2d 1596 (Fed. Cir. 1988), the court pointed out that the PTO has the burden under '103 to establish a *prima facie* case of obviousness and can satisfy this burden only by showing some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references. As noted by the court, whether a particular combination might be "obvious to try" is not a legitimate test of patentability and obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination. The teachings of the prior art must be examined objectively, and not in view of the claimed invention. As further noted by the court, one cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention.

Furthermore, such requirements have been clarified in the decision of *In re Lee*, 61 USPQ 2d 1430 (Fed. Cir. 2002) wherein the court, in reversing an obviousness rejection, indicated that deficiencies of the cited references cannot be remedied with conclusions about what is "basic knowledge" or "common knowledge". The court pointed out:

> The Examiner's conclusory statements that "the demonstration mode is just a programmable feature

> which can be used in many different device[s] for providing automatic introduction by adding the proper programming software" and that "another motivation would be that the automatic demonstration mode is user friendly and it functions as a tutorial" do not adequately address the issue of motivation to combine. This factual question of motivation is immaterial to patentability, and could not be resolved on subjected belief and unknown authority. It is improper, in determining whether a person of ordinary skill would have been led to this combination of references, simply to "[use] that which the inventor taught against its teacher."... Thus, the Board must not only assure that the requisite findings are made, based on evidence of record, but must also explain the reasoning by which the findings are deemed to support the agency's conclusion. (emphasis added)

Independent claim 135 of the instant invention defines a method of identifying a peptide with a desired activity having an indicia that satisfies a test requirement. The method comprises the steps of:

> identifying a predetermined set of peptides;
>
> parameterizing the predetermined set of peptides by:
>
> determining a first parameter for each predetermined peptide, wherein the first parameter is a whole molecule parameter, and
>
> determining a second parameter for each predetermined peptide, wherein the second parameter is dependent on the specific order of constitutive subunits within each predetermined peptide;
>
> performing a space-filling design of the parameterized peptides to identify first test peptides;
>
> constructing a first test peptide library comprising a plurality of first test peptides identified using the space-filling design, wherein the length of said first test peptides comprises about four amino acids to about twenty amino acids, and wherein said first test peptides are a subset of said predetermined set of peptides;
>
> determining an activity, having an indicia, of said plurality of first test peptides;
>
> measuring the indicia of said activity for said plurality of first test peptides;
>
> deriving a quantitative relationship between said indicia of said activity, said first parameter, and said second parameter;

calculating an estimated indicia for each remaining peptide from said predetermined set of peptides using said quantitative relationship;

setting a test requirement, based on a desired activity, having a test indicia range;

selecting a second test peptide library comprising at least one second test peptide, wherein each second test peptide has an estimated indicia that satisfies said test requirement, and wherein said second test peptides are not in said first test peptide library;

measuring the indicia of each second test peptide; and

identifying at least one second test peptide having a measured indicia that satisfies said test requirement.

According to independent claim 135, a predetermined set of peptides is identified and parameterized by determining first and second parameters for each peptide. The first parameter is a whole molecule parameter while the second parameter is dependent on the specific order of constitutive subunits within each peptide. A space-filling design is then performed for the parameterized peptides that will be used in constructing a first test peptide library. Next, each first test peptide is tested so that an indicia can be measured for a desired activity.

According to at least one feature of independent claim 135, a quantitative relationship is derived based on three specific properties of each peptide: the measured indicia, the first parameter, and the second parameter. Once the quantitative relationship is determined, it is applied to calculate (i.e., compute) an estimated indicia for each remaining peptide from the predetermined set of peptides. It is noted that these peptides were not part of the first test peptide library. Furthermore, these peptides were never tested (i.e., assayed or screened). A test requirement is subsequently set based on the desired activity level. The test requirement can be in the form of a range of test indicia values. These values can correspond to a desired range that satisfies a criteria considered to be important.

Next, a second test peptide library containing at least one second test peptide is selected. Only second test peptides having an estimated indicia that has been calculated to satisfy the test requirement are selected to be in the second test peptide library. Since the estimated indicia are calculated only for the remaining peptides, none of the second test peptides are present in the first test peptide library. Furthermore, none of the second test peptides have been tested (e.g., screened or assayed) as this time. At this point, the second test peptides are tested in order to actually measure the indicia. Finally, at least one second test peptide having a measured indicia that satisfies the test requirement is identified.

As previously discussed, Ostrem clearly fails to disclose numerous features recited in independent claim 135. The inclusion of Cramer as a secondary reference does nothing to remedy this shortcoming, since Cramer also fails to disclose or suggest the same features. In addition, Cramer does not appear to even disclose the features recited in claims 83-86, as alleged by the Office Action. Cramer discloses a method of creating and searching a library (i.e., database) of potential molecules using validated molecular structural descriptors. Cramer appears to be concerned only with the database and data structure used to store the records pertaining to the molecules. For example, Cramer illustrates a table which stores a set of properties in an encoded form representative of a shape descriptor. At least one of these properties is indicated as being the hydrophobicity of the molecule. However, Cramer is not concerned with the screening of peptides and/or determination of desired activities. Merely storing the value of this property as a parameter of a data structure cannot be construed as disclosing, or suggesting, any of the claimed features. In fact, Ostrem and Cramer do not even appear to be

properly combinable for arriving at the claimed invention, because neither reference provides any motivation to seek out the teachings of the other with a realistic expectation of arriving at the claimed invention.

Even if Ostrem and Cramer were properly combinable, the combined teachings would be insufficient to render the claimed invention obvious. Cramer provides an overview of the use of compound libraries, while Ostrem provides a description for finding other low molecular weight peptide inhibitors of factor Xa. Neither the combination, nor individual references, teaches a method for identifying peptides having a desired activity.

Accordingly, the combination of Ostrem and Cramer fails to render independent claim 135 obvious under 35 U.S.C. §103(a).

Claims 76, 82-90, and 92-95

Claims 76, 82-90, and 92-95 depend from independent claim 135, and are believed to be allowable for the reasons set forth with respect to independent claim 135.

Independent Claim 136

Independent claim 136 defines a method of identifying a peptide with a desired activity having an indicia that satisfies a test requirement. The method comprises the steps of:

> identifying a predetermined set of peptides;
>
> parameterizing the predetermined set of peptides by:
>
> determining a first parameter for each predetermined peptide, wherein the first parameter is a whole molecule parameter, and

determining a second parameter for each predetermined peptide, wherein the second parameter is dependent on the specific order of constitutive subunits within each predetermined peptide;

performing a space-filling design of the parameterized peptides to identify first test peptides;

constructing a first test peptide library comprising a plurality of first test peptides identified using the space-filling design, wherein the length of said first test peptides comprises about four amino acids to about twenty amino acids, and wherein said first test peptides are a subset of said predetermined set of peptides;

determining an activity, having an indicia, of said plurality of first test peptides;

measuring the indicia of said activity for said plurality of first test peptides;

deriving a quantitative relationship between said indicia of said activity, said first parameter, and said second parameter;

setting a test requirement, based on a desired activity, having a test indicia range;

selecting a subgroup of first test peptides having an indicia that satisfies said test requirement; and

expanding first test peptides from said subgroup into their constituent compound isomers;

performing a space-filling design on said constituent compound isomers to identify candidate peptides;

calculating an estimated indicia for each candidate peptide using said quantitative relationship;

selecting a second test peptide library comprising at least one second test peptide, wherein each second test peptide is a candidate peptide having an estimated indicia that satisfies said test requirement, and wherein said second test peptides are not in said first test peptide library;

measuring the indicia of each second test peptide; and

identifying at least one second test peptide having a measured indicia that satisfies said test requirement.

The Examiner does not raise any new grounds for rejecting this claim. Accordingly, the combination of Ostrem and Cramer still fails to render independent claim 136 obvious under 35 U.S.C. §103(a), since various claim features are neither disclosed nor suggested.

Independent Claim 137

Independent claim 137 defines a method of identifying a peptide with a desired activity having an indicia that satisfies a test requirement. The method comprises the steps of:

> identifying a plurality of initial peptides having a length of about four amino acids to about twenty amino acids;
>
> parameterizing the initial peptides by:
>
> determining a first parameter for each initial peptide, wherein the first parameter is a whole molecule parameter, and
>
> determining a second parameter for each initial peptide, wherein the second parameter is dependent on the specific order of constitutive subunits within each initial peptide;
>
> performing a space-filling design of the parameterized peptides to identify first test peptides;
>
> constructing a first test peptide library comprising a plurality of test peptides identified using the space-filling design, wherein said first test peptides are a subset of said initial peptides;
>
> measuring the indicia of an activity of said plurality of test peptides;
>
> deriving a quantitative relationship between said indicia of said activity, said first parameter, and said second parameter of said plurality of test peptides;
>
> calculating an estimated indicia for each initial peptide using said quantitative relationship;
>
> setting a test requirement, based on a desired activity, said test requirement having a test indicia range;
>
> selecting a second test peptide library comprising at least one second test peptide, wherein each second test peptide has an estimated indicia that satisfies said test requirement, and wherein said second test peptides are not in said first test peptide library;
>
> measuring the indicia of each second test peptide; and
>
> identifying at least one second test peptide having a measured indicia that satisfies said test requirement.

The Examiner does not raise any new grounds for rejecting this claim. Accordingly, the combination of Ostrem and Cramer still fails to render independent

claim 137 obvious under 35 U.S.C. §103(a), since various claim features are neither disclosed nor suggested.

Claims 131, 132, and 134

Claims 131, 132, and 134 depend from independent claim 137, and are believed to be allowable for the reasons set forth with respect to independent claim 137.

Independent Claim 138

Independent claim 138 defines a method of identifying a peptide with a desired activity having an indicia that satisfies a test requirement. The method comprises the steps of:

> identifying a predetermined set of peptides;
>
> parameterizing the predetermined set of peptides by:
>
> determining a first parameter for each predetermined peptide, wherein the first parameter is a whole molecule parameter, and
>
> determining a second parameter for each predetermined peptide, wherein the second parameter is dependent on the specific order of constitutive subunits within each predetermined peptide;
>
> performing a space-filling design of the parameterized peptides to identify first test peptides;
>
> constructing a first test peptide library comprising a plurality of first test peptides identified using the space-filling design, wherein said first test peptides are a subset of said predetermined set of peptides;
>
> determining an activity, having an indicia, of said plurality of first test peptides;
>
> measuring the indicia of said activity for said plurality of first test peptides;
>
> deriving a quantitative relationship between said indicia of said activity, said first parameter, and said second parameter;
>
> calculating an estimated indicia for each remaining peptide from said predetermined set of peptides using said quantitative relationship;

setting a test requirement, based on a desired activity, having a test indicia range;

selecting a second test peptide library comprising at least one second test peptide, wherein each second test peptide has an estimated indicia that satisfies said test requirement, and wherein said second test peptides are not in said first test peptide library;

measuring the indicia of each second test peptide; and

identifying at least one second test peptide having a measured indicia that satisfies said test requirement.

The Examiner does not raise any new grounds for rejecting this claim. Accordingly, the combination of Ostrem and Cramer still fails to render independent claim 136 obvious under 35 U.S.C. §103(a), since various claim features are neither disclosed nor suggested.

CONCLUSION

For the foregoing reasons, the final rejection of the claims should be reversed.

FEES

The Appeal Brief fee has been previously submitted.

AUTHORIZATION

Applicants request any shortage or excess in fees in connection with the filing of this paper, including extension of time fees, and for which no other form of payment is offered, be charged or credited to Deposit Account No. 01-2135 (Case: 1385.45510X00).

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CLAIMS APPENDIX

76. The method of claim 135, wherein said step of deriving a quantitative relationship comprises the step of determining $\hat{y}_i=f(x_{ij})$, where x_{ij} denotes a whole molecule parameter, i ranges from 1 to n where n represents the number of first test peptides in the plurality thereof, j ranges from 1 to d where d represents the number of whole molecule parameters, and $\hat{y}_i$ represents an estimate of the measured indicia of the activity of the plurality of first test peptides.

82. The method of claim 135, wherein said space-filling design expands less than all of the first test peptides into their constituent compound isomers.

83 The method of claim 135, wherein said first parameter is selected from the group consisting of total charge, molecular weight, isoelectric point and total dipole moment.

84. The method of claim 135, wherein said first parameter is selected from the group consisting of total charge, molecular weight, isoelectric point and total dipole moment, and further wherein said second parameter is selected from the group consisting of isotropic surface area, electronic charge index and hydrophobicity.

85. The method of claim 135, wherein said second parameter is selected from the group consisting of isotropic surface area, electronic charge index and hydrophobicity.

86. The method of claim 135, wherein said first parameter is molecular weight and at least one additional parameter is selected from the group consisting of total charge, isoelectric point, total dipole moment, isotropic surface area, electronic charge index, and hydrophobicity.

87. The method of claim 135, wherein the activity is binding to a receptor.

88. The method of claim 135, wherein the activity is enhancement or inducement of a biological activity in a cell.

89. The method of claim 135, wherein the activity is inhibition or prevention of a biological activity in a cell.

90. The method of claim 88 or claim 89, wherein the cell is a cell cultured in vitro.

92. The method of claim 135, wherein the activity is inhibition or prevention of activation of a receptor.

93. The method of claim 135, wherein the activity is enhancement or inducement of activation of a receptor.

94. The method of claim 135, wherein the first test peptide library consists of peptides having a length of no less than four amino acids.

95. The method of claim 135, wherein the first test peptide library consists of peptides having a length of about four to about ten amino acids.

131. The method of claim 137, wherein said step of performing a space-filling design is performed using a space-filling design that applies a distance function.

132. The method of claim 137, wherein the number of initial peptides in said second test peptide library exceeds a predetermined threshold suited for performing said measuring step, and prior to conducting the step of measuring, performing the steps:

selecting a plurality of new peptides from said first test peptide library to form a new test peptide library using a space filling design;

deriving a new quantitative relationship between said measured indicia, said first parameter, and said second parameter;

calculating an estimated indicia for each initial peptide using said new determined relationship;

selecting a new second test peptide library comprising at least one initial peptide having an estimated indicia that satisfies said test requirement; and

repeating said steps of selecting a plurality of new peptides, determining a new relationship, calculating an estimated indicia, and selecting a new second test peptide library until the number of initial peptides in said new second test peptide library does not exceed the predetermined threshold.

134. The method of claim 137, wherein the number of initial peptides in said second test peptide library exceeds a predetermined threshold suited for performing said measuring step, and prior to conducting the step of measuring, performing the steps:

selecting a plurality of new peptides from said first test peptide library to form a new test peptide library using a space filling design;

deriving a new quantitative relationship between said measured indicia, said first parameter, and said second parameter;

calculating an estimated indicia for each initial peptide using said new determined relationship;

selecting a new second test peptide library comprising at least one initial peptide having an estimated indicia that satisfies said test requirement; and

repeating said steps of selecting a plurality of new peptides, determining a new relationship, calculating an estimated indicia, and selecting a new second test peptide library until the measured indicia of at least one of the initial peptides in the second test peptide library satisfies a predetermined threshold.

135. A method of identifying a peptide with a desired activity having an indicia that satisfies a test requirement, the method comprising the steps of:

identifying a predetermined set of peptides;

parameterizing the predetermined set of peptides by:

determining a first parameter for each predetermined peptide, wherein the first parameter is a whole molecule parameter, and

determining a second parameter for each predetermined peptide, wherein the second parameter is dependent on the specific order of constitutive subunits within each predetermined peptide;

performing a space-filling design of the parameterized peptides to identify first test peptides;

constructing a first test peptide library comprising a plurality of first test peptides identified using the space-filling design, wherein the length of said first test peptides comprises about four amino acids to about twenty amino acids, and wherein said first test peptides are a subset of said predetermined set of peptides;

determining an activity, having an indicia, of said plurality of first test peptides;

measuring the indicia of said activity for said plurality of first test peptides;

deriving a quantitative relationship between said indicia of said activity, said first parameter, and said second parameter;

calculating an estimated indicia for each remaining peptide from said predetermined set of peptides using said quantitative relationship;

setting a test requirement, based on a desired activity, having a test indicia range;

selecting a second test peptide library comprising at least one second test peptide, wherein each second test peptide has an estimated indicia that satisfies

said test requirement, and wherein said second test peptides are not in said first test peptide library;

measuring the indicia of each second test peptide; and

identifying at least one second test peptide having a measured indicia that satisfies said test requirement.

136. A method of identifying a peptide with a desired activity having an indicia that satisfies a test requirement, the method comprising the steps of:

identifying a predetermined set of peptides;

parameterizing the predetermined set of peptides by:

determining a first parameter for each predetermined peptide, wherein the first parameter is a whole molecule parameter, and

determining a second parameter for each predetermined peptide, wherein the second parameter is dependent on the specific order of constitutive subunits within each predetermined peptide;

performing a space-filling design of the parameterized peptides to identify first test peptides;

constructing a first test peptide library comprising a plurality of first test peptides identified using the space-filling design, wherein the length of said first test peptides comprises about four amino acids to about twenty amino acids, and wherein said first test peptides are a subset of said predetermined set of peptides;

determining an activity, having an indicia, of said plurality of first test peptides;

measuring the indicia of said activity for said plurality of first test peptides;

deriving a quantitative relationship between said indicia of said activity, said first parameter, and said second parameter;

setting a test requirement, based on a desired activity, having a test indicia range;

selecting a subgroup of first test peptides having an indicia that satisfies said test requirement; and

expanding first test peptides from said subgroup into their constituent compound isomers;

performing a space-filling design on said constituent compound isomers to identify candidate peptides;

calculating an estimated indicia for each candidate peptide using said quantitative relationship;

selecting a second test peptide library comprising at least one second test peptide, wherein each second test peptide is a candidate peptide having an estimated indicia that satisfies said test requirement, and wherein said second test peptides are not in said first test peptide library;

measuring the indicia of each second test peptide; and

identifying at least one second test peptide having a measured indicia that satisfies said test requirement.

137. A method of identifying a peptide with a desired activity having an indicia that satisfies a test requirement, the method comprising the steps of:

identifying a plurality of initial peptides having a length of about four amino acids to about twenty amino acids;

parameterizing the initial peptides by:

determining a first parameter for each initial peptide, wherein the first parameter is a whole molecule parameter, and

determining a second parameter for each initial peptide, wherein the second parameter is dependent on the specific order of constitutive subunits within each initial peptide;

performing a space-filling design of the parameterized peptides to identify first test peptides;

constructing a first test peptide library comprising a plurality of test peptides identified using the space-filling design, wherein said first test peptides are a subset of said initial peptides;

measuring the indicia of an activity of said plurality of test peptides;

deriving a quantitative relationship between said indicia of said activity, said first parameter, and said second parameter of said plurality of test peptides;

calculating an estimated indicia for each initial peptide using said quantitative relationship;

setting a test requirement, based on a desired activity, said test requirement having a test indicia range;

selecting a second test peptide library comprising at least one second test peptide, wherein each second test peptide has an estimated indicia that satisfies said test requirement, and wherein said second test peptides are not in said first test peptide library;

measuring the indicia of each second test peptide; and

identifying at least one second test peptide having a measured indicia that satisfies said test requirement.

138. A method of identifying a peptide with a desired activity having an indicia that satisfies a test requirement, the method comprising the steps of:

identifying a predetermined set of peptides;

parameterizing the predetermined set of peptides by:

determining a first parameter for each predetermined peptide, wherein the first parameter is a whole molecule parameter, and

determining a second parameter for each predetermined peptide, wherein the second parameter is dependent on the specific order of constitutive subunits within each predetermined peptide;

performing a space-filling design of the parameterized peptides to identify first test peptides;

constructing a first test peptide library comprising a plurality of first test peptides identified using the space-filling design, wherein said first test peptides are a subset of said predetermined set of peptides;

determining an activity, having an indicia, of said plurality of first test peptides;

measuring the indicia of said activity for said plurality of first test peptides;

deriving a quantitative relationship between said indicia of said activity, said first parameter, and said second parameter;

calculating an estimated indicia for each remaining peptide from said predetermined set of peptides using said quantitative relationship;

setting a test requirement, based on a desired activity, having a test indicia range;

selecting a second test peptide library comprising at least one second test peptide, wherein each second test peptide has an estimated indicia that satisfies said test requirement, and wherein said second test peptides are not in said first test peptide library;

measuring the indicia of each second test peptide; and

identifying at least one second test peptide having a measured indicia that satisfies said test requirement.

EVIDENCE APPENDIX

None

RELATED PROCEEDINGS APPENDIX

None